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Factors associated with intrahepatic cholestasis of pregnancy and its influence on maternal and infant outcomes

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Abstract

The aim of this study was to investigate the clinical features and risk factors of intrahepatic cholestasis of pregnancy (ICP) and its effect on pregnancy outcomes. The data from 300 pregnant women with ICP and 300 pregnant women without ICP admitted from July 2015 to December 2016 at Changsha Maternal and Child Health Hospital were collected. The factors associated with ICP were examined. The family history of ICP, twin pregnancies, number of births, hypertensive disorder of pregnancy (HDP), gestational diabetes, hyperlipidemia, hepatitis virus infection, and in vitro fertilization and embryo transfer, differed significantly between the 2 groups (all $P < .05$). The multivariable analysis showed that body mass index at delivery, number of births, HDP, gestational diabetes, hyperlipidemia, and hepatitis virus infection were associated with ICP (all $P < .05$). The incidence of abnormal amniotic fluid and premature births in the ICP group were significantly higher than in the control group (all $P < .05$). ICP is associated with BMI at delivery, number of births, HDP, gestational diabetes, hyperlipidemia, and hepatitis virus infection. ICP greatly influences pregnancy outcomes.

Abbreviations: BMI = body mass index, HDP = hypertensive disorder of pregnancy, ICP = intrahepatic cholestasis of pregnancy, IVF-ET = in vitro fertilization and embryo transfer, TBA = total bile acid.

Keywords: blood loss, intrahepatic cholestasis of pregnancy, pregnancy outcome, risk factors, total bile acids

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is a reversible hepatic disorder occurring in the late second and early third trimesters of pregnancy.[1] It mainly features pruritus, elevated serum bile acids, and liver function abnormalities.[2] Although the etiology of ICP is not completely understood, genetic, endocrine, and environmental factors are likely involved.[3] Known risk factors for ICP include a previous history of ICP, chronic liver disease, chronic hepatitis C, multifetal pregnancy, and advanced maternal age.[4]

ICP occurs in 0.2% to 2% of all pregnancies, and its incidence varies with ethnicity and geographic location.[5] For example, ICP incidence is elevated in South American (9.2%-15.6%) and Scandinavian nations (1.5%) compared with Europe (0.1%-0.2%), and 0.2% to 0.3% of pregnancies in the USA are affected.[6]

The maternal outcomes are generally benign, but ICP increases the risk of adverse obstetrical outcomes, including stillbirth, respiratory distress syndrome, meconium passage, and fetal asphyxiation, with perinatal morbidity and mortality.[7,8]

Despite the available knowledge, the specific features of ICP in China remain undefined. Therefore, the present retrospective study investigated the clinical characteristics and outcomes of ICP from 2015 to 2016 in the drainage areas of the Yangtze River in China, which includes Changsha City. The factors associated with ICP and the impact of ICP on pregnancy outcomes were analyzed. The results could help improve the management of ICP.

2. Materials and Methods

2.1. General information

Between July 2015 and December 2016, 300 pregnant women with ICP and 15,306 patients with normal pregnancies were hospitalized for delivery at Changsha Maternal and

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The Ethics Committee of Changsha Maternal and Child Health Hospital approved this study. The requirement for individual consent was waived by the committee because of the retrospective nature of the study. This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association.

The authors certify that their manuscript is a unique submission and is not being considered for publication by any other source in any medium.

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Key points

What is already known on this subject?

Known risk factors for intrahepatic cholestasis of pregnancy (ICP) include a previous history of ICP, chronic liver disease, chronic hepatitis C, multifetal pregnancy, and advanced maternal age. Its incidence varies with ethnicity and geographic location. The maternal outcome is generally benign, but ICP increases the risk of adverse obstetrical outcomes. Still, the specific features of ICP in China remain undefined.

What the results of this study add?

The present retrospective study aimed to investigate the clinical characteristics and outcomes of ICP from 2015 to 2016 in the Yangtze River area (China), which includes Changsha City. The factors associated with ICP were collected to analyze the impact of ICP on pregnancy outcomes. The findings indicate that ICP is closely related to BMI at delivery, the number of births, HDP, gestational diabetes, hyperlipidemia, and hepatitis virus infection. ICP is also associated with the occurrence of abnormal amniotic fluid and premature births.

What the implications are of these findings for clinical practice and/or further research?

The incidence of ICP has obvious differences among different regions and races and in relation to dietary habits. Its pathogenesis is relatively complex. The results could help improve the management of ICP in China.

Child Health Hospital. The prevalence of ICP in the study population during this period was 1.96%. Among the non-ICP women, 300 were selected as the controls. This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. The Ethics Committee of Changsha Maternal and Child Health Hospital approved this study. The requirement for individual consent was waived by the committee because of the retrospective nature of the study.

The inclusion criteria were meeting the diagnostic criteria for ICP according to ICP Diagnosis and Treatment Guide (2015) formulated by the obstetrics Group of the Chinese Society of Obstetrics and Gynecology, pregnant women in the middle and late stages of pregnancy, stable condition, and complete clinical data. The diagnostic criteria were skin pruritus that could not be explained by other reasons and that mainly involved the palms and soles of feet (skin scratching caused by severe skin itching needed to be differentiated from other pregnancy skin diseases), fasting blood total bile acid (TBA) ≥ 10 μmol/L, normal bile acid levels that were accompanied by liver function abnormalities that could not be explained by other reasons (mainly mild to moderately elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels; the level of γ-glutamyl transferase (GGT) could also be increased, and accompanied by increased serum bilirubin (TBIL) levels, mainly direct bilirubin (DBIL) levels), and pruritus usually subsided 1 to 2 days after delivery and liver function indexes that returned to normal 4 to 6 weeks after delivery.

The exclusion criteria were severe heart, liver, brain, kidney, and other organ diseases, mental illness and communication disorders, or incomplete obstetric examination data. The pregnant women in the ICP group were 19 to 42 (average, 28.09 ± 4.00) years old. The average body mass index (BMI) at delivery was 26.47 ± 3.01 kg/m^2.

The patients with ICP were divided into mild and severe ICP. The criteria for mild ICP were serum TBA ≥ 10-40 μmol/L, and the main clinical symptoms included skin pruritus without obvious other symptoms. The criteria for severe ICP were serum TBA ≥ 40 μmol/L, clinical symptoms included severe itching, accompanied by other conditions, such as multiple pregnancies, hypertensive disorder of pregnancy (HDP), recurrent ICP, and perinatal death due to ICP, and early-onset ICP (i.e., before 28 weeks).[9] There is no international ICP classification based on the onset time; however, early-onset patients had worse perinatal outcomes and were classified as severe ICP.

In addition, 300 pregnant women without ICP admitted during the same period were randomly selected as the control group. They were 20 to 33 (average, 27.30 ± 2.51) years old. The average BMI at delivery was 25.49 ± 2.02 kg/m^2.

2.2. Research methods

The clinical data of pregnant women in the ICP and control groups were collected retrospectively. The data included age, number of pregnancies, number of births, BMI at delivery, gestational age at delivery, family history of ICP, number of miscarriages, hepatitis virus infection, twin pregnancy, HDP, gestational diabetes, hyperlipidemia, fetal distress, amniotic fluid contamination, postpartum hemorrhage, premature birth, and neonatal asphyxia.

2.3. Statistical analysis

The SPSS 19.0 statistical software was used for data processing. The measurement data were expressed as mean ± standard deviation. The categorical data were expressed as frequency. One-way ANOVA was used to compare measurement data among multiple groups. The independent sample *t* test was used for comparison between the 2 groups. The chi-square test was used for the categorical data. Logistic regression analysis was used to identify the factors independently associated with ICP. $P < .05$ was considered statistically significant.

3. Results

3.1. Univariable analyses of factors affecting the occurrence of ICP

There were statistically significant age differences, BMI at delivery, family history of ICP, twin pregnancies, number of births, HDP, gestational diabetes, hyperlipidemia, hepatitis virus infection, and in vitro fertilization and embryo transfer (IVF-ET) between the 2 groups, as shown in Table 1.

3.2. Multivariable analysis of factors affecting the occurrence of ICP

ICP was the dependent variable in the multivariable analysis (control group = 0, ICP group = 1), while the variables significantly different in the univariable analyses were used as the independent variables. The multivariable analysis was performed by stepwise logistic regression. It showed that the factors associated with ICP included BMI at delivery, the number of births, HDP, gestational diabetes, hyperlipidemia, and hepatitis virus infection ($P < .05$), as shown in Table 2.

3.3. Comparison of pregnancy outcomes between the 2 groups

The occurrence of abnormal amniotic fluid and premature birth in the ICP group were significantly higher than in the control group (both $P < .05$), as shown in Table 3.

Table 1

Univariable analysis of factors affecting the occurrence of ICP.

	Normal group (n = 300)	ICP group (n = 300)	x^2/t	P
Age	27.30 ± 2.51	28.09 ± 4.00	2.886	.004
BMI at delivery	25.49 ± 2.02	26.47 ± 3.01	4.684	<.001
Family history of ICP	0 (0)	10 (3.33)	10.169	.001
Twin pregnancy	5 (1.67)	23 (7.67)	12.138	<.001
Miscarriage times ≥ 2	78 (26.00)	77 (25.67)	0.009	.926
Number of births			19.632	<.001
Primiparous	263 (87.67)	220 (73.33)		
Parous	37 (12.33)	80 (26.67)		
HDP	2 (0.67)	24 (8)	19.459	<.001
Gestational diabetes	13 (4.33)	40 (13.33)	15.087	<.001
Hyperlipidemia	11 (3.67)	30 (10)	9.451	.002
Hepatitis virus infection	8 (2.67)	49 (16.33)	32.587	<.001
IVF-ET	5 (1.67)	22 (7.33)	11.208	.001

BMI = body mass index, HDP = hypertensive disorder of pregnancy, ICP = intrahepatic cholestasis, IVF-ET = in vitro fertilization and embryo transfer.

Table 2

Multivariable logistic regression of factors affecting the occurrence of ICP.

							95% CI of OR	
Variables/indexes	B	SE	Wald	df	P	OR	Lower limit	Upper limit
Age	0.027	0.029	0.857	1	.354	1.027	0.970	1.088
BMI at delivery	0.092	0.038	5.963	1	.015	1.096	1.018	1.180
Twin pregnancy	0.718	0.689	1.085	1	.298	2.051	0.531	7.921
Number of births	0.867	0.247	12.327	1	<.001	2.379	1.467	3.860
HDP	2.702	0.756	12.773	1	<.001	14.911	3.388	65.625
Gestational diabetes	1.146	0.351	10.665	1	.001	3.146	1.581	6.260
Hyperlipidemia	1.193	0.385	9.607	1	.002	3.295	1.550	7.005
Hepatitis virus infection	1.999	0.404	24.461	1	<.001	7.379	3.342	16.291
IVF-ET	0.673	0.709	0.901	1	.342	1.961	0.488	7.870
Constant	−4.617	1.221	14.292	1	<.001	0.010		

B = regression coefficient, BMI = body mass index, CI = confidence interval, df = degree of freedom, HDP = hypertensive disorder of pregnancy, ICP = intrahepatic cholestasis, IVF-ET = in vitro fertilization and embryo transfer, OR = odds ratio, SE = standard error, Wald = Chi-square value.

Table 3

Comparison of the complications between the 2 groups [cases (%)].

Group	n	Abnormal amniotic fluid	Premature birth	Postpartum hemorrhage
Normal group	300	11 (3.67)	6 (2.00)	2 (0.67)
ICP group	300	34 (11.33)	80 (26.67)	3 (1.00)
x^2		12.709	74.328	0.202
P		<.001	<.001	.653

ICP = intrahepatic cholestasis.

3.4. Comparison of the pregnancy outcomes among groups

The differences in final gestational weeks and days of hospitalization between different ICP levels were statistically significant. The final gestational week of severe ICP was smaller than in mild ICP, and the final gestational week of mild ICP was smaller than in the normal group. The hospitalization days of mild ICP and severe ICP were higher than in the normal group, and there was no significant difference in the amount of bleeding between different ICP levels, as shown in Table 4.

4. Discussion

The incidence of ICP has obvious differences in different regions and races and in relation to dietary habits.[5,6] Its pathogenesis is relatively complex, and scholars generally believe that it is related to factors such as genetics, endocrine, immune disorders, and selenium deficiency.[10–13] The results showed that a family history of ICP had an impact on the occurrence of ICP. Previous studies have pointed out that genetics is a fundamental factor affecting estrogen levels and bile metabolism, and people carrying an ICP susceptibility gene (e.g., mutated ABCB4 gene[14]) are more prone to ICP.[15] The present study showed that twin pregnancy was associated with the occurrence of ICP, which may be because women pregnant with twins had higher estrogen levels and aggravated abnormal lipid metabolism than single pregnancies, thus increasing the possibility of cholestasis.

TBA is the most important basis for the clinical diagnosis of ICP and the most significant laboratory evidence for the diagnosis of ICP. In this study, TBA grouping mainly referred to the diagnostic criteria of ICP diagnosis and treatment pregnancy guidelines from 2015, and it included the mild ICP group (TBA ≥ 10-40 μmol/L) and the severe ICP group (TBA ≥ 40 μmol/L). The results showed that the final gestational week in severe ICP occurred earlier than in mild ICP, and the final gestational week of mild ICP occurred earlier than in normal pregnancies. There were no significant differences in bleeding among different ICP degrees. The increase of TBA inhibits the secretion of vascular endothelial cell growth factor by vascular endothelial cells and trophoblast cells and affects the formation of placental blood vessels and the growth and development of fetal organs and tissues. It also causes placental villi surface vasospasms, increases the vascular resistance of the villus venous, promotes fetal intestinal peristalsis, and increases the rate of amniotic fluid pollution. At the same time, bile acids could also

Table 4

Comparison of indicators between different ICP levels.

Index	Normal group (n = 300)	Mild ICP (n = 223)	Severe ICP (n = 77)	x^2/F	*P*
Final gestational weeks	38.62 ± 0.99	37.35 ± 2.40*	36.56 ± 2.02*†	57.079	<.001
Amount of bleeding	242.17 ± 84.19	235.87 ± 112.67	254.55 ± 93.61	1.081	.340
Neonatal asphyxia	0 (0.00)	2 (0.90)	1 (1.30)	3.201	.202
Hospitalization days	2.73 ± 0.74	5.31 ± 3.41*	5.92 ± 4.18*	84.255	<.001

ICP = intrahepatic cholestasis.

* $P < .05$ compared with the normal group.

† $P < .05$ compared with the mild ICP.

promote the release of prostaglandins and induce premature delivery of ICP in pregnant women.

It was previously reported that ICP was associated with maternal complications, including HDP, gestational diabetes, and hyperlipidemia.[16–19] This study showed that HDP was independently associated with ICP (OR = 14.911), consistent with the literature. As a common complication during pregnancy, the basic pathological changes of HDP mainly include systemic arteriole spasm, which leads to a reduced oxygen supply, causing vascular endothelial cell damage and damage to the heart and brain. When ICP and hypertension are combined, the 2 affect each other, the spasms of the small arteries increase the accumulation of bile acids, decrease the oxygen supply function of the placenta, and restrict fetal growth, resulting in intrauterine hypoxia and fetal distress. In serious cases, fetal or neonatal death and other adverse outcomes can occur. As mentioned in a previous study,[20] if ICP and HDP are clinically complicated, the probability of neonatal asphyxia and fetal death greatly increases. Therefore, timely treatment of hypertension in ICP patients is necessary for clinical practice to minimize the incidence of adverse fetal outcomes.

ICP may also be related to metabolic abnormalities in affected women.[21] In a retrospective case-control study that included 57,724 pregnancies from February 2005 to June 2011, Martineau et al[16] reported 143 cases of combined ICP (0.25%), 4880 cases with gestational diabetes (8.5%), and 19 cases with both ICP and gestational diabetes. Moreover, in all patients with ICP, the incidence of gestational diabetes was 13.4% before the onset of ICP, and the incidence of gestational diabetes increased to 30% after the onset of ICP, thus indicating that ICP can increase the risk of gestational diabetes in pregnant women. This study showed that gestational diabetes could lead to an increased incidence of ICP, and gestational diabetes was independently associated with ICP (OR = 3.146). The interaction between abnormal blood glucose and ICP could further aggravate the liver injury, leading to adverse pregnancy outcomes. When ICP is combined with diabetes, fetal hyperinsulinemia might antagonize adrenalin and inhibit the synthesis of alveolar surfactant, which might delay fetal lung maturation. Conversely, the high blood glucose levels of patients with gestational diabetes increase the degree of coagulation, platelet activation, and fibrinogen level, which could lead to vascular endothelial cell proliferation, basement membrane thickening, and lumen stenosis, eventually leading to microvascular lesions. The above-mentioned pathological changes of the placenta can decrease placental blood perfusion, resulting in an increased incidence of premature delivery, amniotic fluid contamination, neonatal asphyxia, and respiratory distress syndrome, making clinical treatment more difficult and neonatal outcomes unpredictable.[17] Therefore, age-appropriate pregnancy, control of pre-pregnancy and gestational weight, timely detection of gestational diabetes, and strict control of blood sugar are also essential for preventing adverse fetal outcomes in pregnant women with ICP.

A certain correlation between the incidence of ICP and abnormal lipid metabolism in the body has been observed.[22] Zhang et al[23] explored the differential metabolic profile of the placenta in patients with ICP, and their bioinformatics analysis revealed significant changes in lipid metabolism pathways in ICP. In this study, hyperlipidemia was independently associated with ICP (OR = 3.295). A population survey study showed that high triglyceride levels (TG) in the second trimester were significantly associated with ICP, and hypertriglyceridemia could be considered an important predictor of ICP. Moreover, every 1 mmol/L increase in serum TG concentration in women in the third trimester increases the risk of ICP.[22]

Hepatitis virus infection is closely correlated with the occurrence of ICP.[24] This study showed that combined hepatitis virus infection was independently associated with ICP (OR = 7.379), consistent with the previous study. Hepatitis infection affects immune cells, such as natural killer cells and T cells, resulting in abnormal liver function and bile acid metabolism,[25,26] which eventually leads to bile salt metabolism disorder, significantly increasing the levels of bilirubin and bile acid.

ICP was found to be an indication of high-risk pregnancy and to have a significant impact on pregnancy outcomes.[7,27,28] Cai[29] pointed out that every increase of 1.0 μmol/L of TBA in maternal serum would increase the risk of intrauterine distress in perinatal infants by 0.2‰. In this study, we compared the pregnancy outcomes of pregnant women with ICP and healthy pregnant women. Both amniotic fluid pollution and preterm birth in the ICP group were higher than in the control group, indicating that ICP could increase the rate of preterm birth and increase amniotic fluid pollution in pregnant women. It may be due to the high TBA levels that could upregulate the levels of oxytocin and its receptors in the fetal membrane, promote the secretion of prostaglandin by the placenta and enhance the sensitivity of the myometrium to oxytocin, thereby causing premature birth.[30,31] Results of the perinatal infants in this study showed that the incidence of amniotic contamination in the ICP group was higher than in the control group. TBA could enter the fetus through the umbilical cord blood, stimulate the long smooth muscle, and promote meconium discharge into the amniotic fluid, resulting in contamination and turbidity.[7] A previous study[32] reported that umbilical cord blood contaminated by meconium could cause ulcers and necrosis, resulting in an acute reduction of umbilical cord blood flow, intrauterine hypoxia, and even fetal death.

This study revealed that ICP did not increase the incidence of postpartum hemorrhage. The following measures can be taken to improve the adverse outcomes for mothers and infants. Close monitoring of the intrauterine situation of the fetus and timely termination of pregnancy. Close monitoring of the liver function indexes of ICP patients, timely symptomatic treatment for liver protection, and prevention of postpartum hemorrhage. There are still no general consensuses on the timing of delivery in pregnant women with ICP, and some studies suggested that excessive intervention in the delivery of ICP pregnant women could lead to an increase in the rate of cesarean sections. Therefore, medical staff should comprehensively weigh the advantages and disadvantages and guide patients to choose the right time and way of delivery according to their specific situation.

This study had limitations. It was a retrospective analysis, and the sample size was small. In addition, there are no multicenter studies on the factors affecting ICP. The study was retrospective and limited to the data available in the charts. Future prospective and multicenter studies with expanded sample sizes are needed to validate the reported findings further.

In conclusion, family history of ICP, multiple pregnancies, BMI at delivery, number of births, combined HDP, gestational diabetes, hyperlipidemia, and hepatitis virus infection are independently associated with ICP. ICP can lead to perinatal amniotic fluid pollution and increased premature birth but does not increase the incidence of postpartum hemorrhage.

Author contributions

Ping Li contributed to the conception and design, supervision, funding, materials, data collection and analysis, and literature review, and drafted and critically revised the manuscript. Yabing Tang and Yurong Jiang contributed to the conception and design, supervision, data collection, and processing and helped to draft and revise the manuscript. Mina Xie was responsible for materials, data collection, analysis, and literature review. Yiping You participated in conception, design, and supervision. All authors read and approved the final manuscript.
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